Recent research has shown that antipsychotic medications may be able to affect the natural course of schizophrenia, particularly when given early during the course of the illness. This suggests that antipsychotic medications may prevent disease progression in schizophrenia by a mechanism that is yet to be identified.

Acute-phase efficacy results suggest that few differences in therapeutic efficacy exist between individual or classes of antipsychotic medications. Fewer studies have examined the comparative effectiveness of antipsychotic drugs in first-episode psychosis and whether the initial exposure to one medication or another would also be manifest in first-episode schizophrenia. We tested this hypothesis in a sample of first-episode, antipsychotic-naive individuals by randomising them to clozapine or chlorpromazine with long-term follow-up. The 52-week outcome results have been reported previously: we found that treatment with clozapine led to greater efficacy after 12 weeks of inpatient treatment, faster time to remission and greater time in remission, however, by 52 weeks these efficacy differences were no longer observed. No outcome results from that trial beyond 1 year have been reported. In this paper, we report the 9-year follow-up results. We hypothesised that individuals originally randomised to clozapine as their first treatment exposure would have better long-term outcomes than those who were originally randomised to chlorpromazine, with the understanding that the majority of individuals would probably have taken several medications other than clozapine or chlorpromazine by the end of the study.
Participants
A detailed description of the design for this study has been published previously. This study was designed by the senior authors (J.A.L. and M.R.P.) and conducted at the Beijing Suicide Research and Prevention Center at the Beijing Hui Long Guan Hospital. It was approved by the Research Review Board of the Beijing Bureau of Health and conformed to the international standards for research ethics. All hospital admissions between October 1995 and December 1998 were screened for inclusion in this study. Inclusion criteria were: age between 16 and 40 years, diagnosis of schizophrenia or schizophreniform disorder, no previous antipsychotic treatment or a maximum of 14 days of prior use, maximum symptom duration of 60 months, current psychotic symptoms of moderate severity or greater for at least one of the five psychotic items assessed by the Brief Psychiatric Rating Scale (BPRS). Written informed consent was provided by individuals and their families for those individuals who met the preceding criteria.

Diagnoses were established with a Chinese version of the Structured Clinical Interview for DSM–IV Axis I disorders, along with blood tests and physical examinations. Participants were initially randomised to either clozapine with a placebo benzotropine or chlorpromazine with benzotropine (2 mg twice daily) while in the hospital. For randomisation, the study nurse stratified eligible in-patients into six groups by gender and duration of positive symptoms (3–9 months, 9–24 months and 24–60 months). Participants in each of these six strata were randomised in blocks of four to either the clozapine or chlorpromazine treatment group. Participants remained in the hospital for 12 weeks, after which they were followed monthly as out-patients. They were maintained on their assigned medication under double-blind conditions for 2 years or up to the point that there was a clinical indication to change their medication regimen, whichever came first. After this point all participants were treated in an open-label, naturalistic manner. Treatment adherence was monitored via pill counting during both the randomised and open-label phases of the study.

Assessments
Efficacy assessments were performed at study entry, weekly for weeks 1–6, biweekly for weeks 6–12, at hospital discharge and every 3 months thereafter. Assessments included the Chinese versions of the BPRS, the Scale for the Assessment of Negative Symptoms (SANS), the Clinical Global Impression Scale (CGI) and the Global Assessment of Functioning Scale (GAF). To assess side-effects, we used the Simpson Angus Extrapyramidal Symptoms Scale (SAESS) (omitting saliorrhea given the use of clozapine in this trial) on the same schedule for the first 2 years and then every 6 months thereafter; and classification terms from the Coding Symbol and Thesaurus for Adverse Event Terminology (COSTART) at each assessment visit for the first year, every 3 months for the second and third years, and every 6 months thereafter. We assessed for tardive dyskinesia using the Tardive Dyskinesia Rating Scale. At periodic intervals two clinicians independently assessed participants, which allowed for verification of ratings. Electrocardiograms (ECGs) were performed at study entry, weeks 12 and 52 and yearly thereafter. White blood cell counts were done weekly during the in-patient phase of the study (i.e. approximately 12 weeks), monthly for the remainder of year 1 and year 2, and every 3 months thereafter. Fasting blood glucose values were assessed at study entry, week 12, every 3 months for the remainder of the first year and every 6 months thereafter. Weight was not regularly assessed during this study, so our analysis (see statistical methods below) only included weights for the 29 participants for whom we were able to calculate weight change. Additionally, the occurrence of seizures was not formally assessed during this study. However, none was reported in either group.

Statistical methods
Our primary analysis compared treatment efficacy for clozapine vs. chlorpromazine for schizophrenia, following the intent-to-treat principle to compare patient outcomes according to the initial treatment assignment. Our primary analytical strategy employed generalised linear mixed models (GLMMs) for categorical repeated measures such as remission status, and mixed-effect models for continuous repeated measures such as the BPRS, SANS, CGI and GAF. The inference from these models is valid provided that the missing data are ‘missing at random’.

Following our previous publication from this study, the primary outcome measure was participant’s remission status over the course of the 9-year observation period, classified into three ad hoc clinical states: remission, intermediate state and relapse. Remission was defined as a reduction in the total BPRS score of 50% or more from baseline, with scores of mild (3) or less on all five BPRS psychotic items (unusual thought content, suspiciousness, hallucinations, conceptual disorganisation, mannerisms and posturing) and a CGI-S severity item of mild (3) or less. Relapse was defined as having at least one BPRS psychotic item scored moderately severe (5) or higher, or at least two BPRS psychotic items scored moderate (4) or higher. The intermediate state was defined as everything else.

A three-category GLMM with logistic links was specified for the remission status as a function of initial treatment assignment, time, and other baseline covariates: baseline BPRS, CGI and GAF, which were all treated as continuous measures, were estimated and tested using an approach similar to that described above.

The effect of initial treatment assignment on participants’ time to dropout (retention) and the time to stopping study medication was examined using Kaplan–Meier estimates for the respective survival curves, and tested using log-rank tests. This analysis was expanded further using a Cox proportional hazards model to adjust for the covariates listed above. We used Fisher’s exact test to compare the proportions of individuals in each group who remained in the study after 9 years, the proportions of individuals in each group who remained on the originally assigned study medication, and the proportion of individuals who switched from chlorpromazine to clozapine or vice versa. Individuals who stopped taking their originally assigned medication for less than 3 months and then resumed the same medication were not considered to have discontinued their study medication unless they were treated with another antipsychotic medication.

We used t-tests to compare the average percentage of time on any antipsychotic medication after the first year, the average dose of antipsychotic medications in terms of chlorpromazine equivalents between year 2 and year 9, and the average dose of antipsychotic medications after the first year during days on which antipsychotic medications were taken (clozapine doses were converted to chlorpromazine equivalents by multiplying the clozapine dose by 1.33). The effect of cumulative antipsychotic
dosage on the improvement of the BPRS from year 2 through year 9 or drop-out was compared for the two treatments using a linear regression model adjusted for several baseline covariates: baseline BPRS score, participant gender, DUP and age at onset of psychosis. We also examined the average percentages of time that individuals in each group took various antipsychotic medications after discontinuing the originally assigned study medication.

We used Fisher’s exact test to compare the proportions of participants who developed tardive dyskinesia and agranulocytosis (absolute neutrophil count <500) for the two treatment groups, and the proportion of individuals who developed tardive dyskinesia, along with mean weight gain, for participants who remained on the originally assigned study medications for 9 years. Tardive dyskinesia was liberally defined as a score of ≥2 on any body part subscale from a version of the Tardive Dyskinesia Rating Scale.32

Analysis of covariance (ANCOVA) models were used to test the differences in laboratory parameters at the end of the study (percentage of neutrophils and lymphocytes, white blood cells, glucose, heart rate and ECG QT interval) between the two treatments after controlling for baseline BPRS, participant gender, DUP and age at onset of psychosis. Some of the laboratory measures were not collected at the end of the study, so we filled in the missing values (n = 5 for weight gain and n = 1 for glucose) with regression-based extrapolations. Finally, for demographic and clinical variables, Fisher’s exact test was used for categorical variables and t-test was used for continuous variables. All tests used a two-sided alpha-level of 0.05.

Results

Participants

The demographic and clinical data for the participants in this study have been previously published.25 Briefly, there were no statistically significant differences between the participants in the clozapine and chlorpromazine groups on any demographic variable (i.e. diagnosis, age, gender, baseline symptom severity and duration, and age at onset of psychotic symptoms; see online Table DS1 for the between-group analyses for those variables used later in this analysis for which results were adjusted). The average age of participants at study entry was 28.7 years (s.d. = 6.9) with a range of 15 to 42. The majority of individuals were diagnosed with paranoid schizophrenia (53%), and the rest with either undifferentiated schizophrenia (23%) or schizoaffective disorder (24%). Participants experienced psychotic symptoms for an average of 18.4 months (s.d. = 17.8 months, median 10.7) at the time of study entry. The mean age at onset of psychotic symptoms was 27.2 years (s.d. = 6.5 years, median 26.9). The mean baseline symptom severity scores were 43.8 (s.d. = 5.1) for total BPRS, 5.6 (s.d. = 0.6) for CGI-severity and 35.8 (s.d. = 7.8) for GAF.

Retention and treatment status

The first-year outcome data have been reported previously.25 Figure 1 presents the flow of participants in this study. Of the 160 participants who initially received treatment with clozapine (n = 80) or chlorpromazine (n = 80), 124 (77.5%) continued to be followed in the study for 9 years, 63 in the clozapine group (79%) and 61 in the chlorpromazine group (76%) (P = 0.85). There was no statistically significant difference in time to drop-out between the two groups (P = 0.71) (Fig. 2). This outcome remained statistically insignificant after using a Cox proportional hazard regression analysis to adjust for baseline total BPRS score, age at onset of psychotic symptoms, gender and DUP. Of the 36 individuals who dropped out of the study during the 9-year period, 19 (clozapine 9; chlorpromazine 10) dropped out during the first year. (Notably, this result is different from that reported in the initial report25 because in the current analysis drop-out was defined as leaving the study, whereas in the original analysis drop-out included individuals who discontinued the medication to which they were originally randomised but continued to be followed-up by study staff.) Reasons for drop-out from the study included: for the clozapine group – withdrew consent 6, adverse effects 1, lack of efficacy 0, death 2, lost to follow-up 7, elopement from the hospital 1, imprisonment 0; for the chlorpromazine group – withdrew consent 6, adverse effects 1, lack of efficacy 1, death 2, lost to follow-up 8, elopement from the hospital 0, imprisonment 1. The causes of the four deaths were viral encephalitis (or meningitis), accident, unknown illness and suicide. Overall, the mortality rates were 2.5% (2/80) in both treatment groups.

Twenty-nine participants (18%) remained on the originally assigned medication after 9 years, 21 in the clozapine group (26%) and 8 in the chlorpromazine group (10%) (P = 0.01). The median amount of time until first discontinuation of the originally assigned study medication was 39 months in the clozapine group and 23 months in the chlorpromazine group, a statistically significant advantage for clozapine (log-rank 7.49, d.f. = 1, P = 0.01) (Fig. 3). The result was similar when examined using a Cox proportional hazard regression to adjust for baseline total BPRS score, age at onset of psychotic symptoms, gender and DUP (hazard ratio 0.644, 95% CI 0.45–0.92, P = 0.01). Among individuals who remained in the study after 1 year (n = 70 for clozapine, 69 for chlorpromazine), there was a non-significant trend for those in the clozapine group to spend more time (in terms of cumulative percentage of days) on any antipsychotic medication than those in the chlorpromazine group (77% v. 66%, t(137) = −1.82, P = 0.07), whereas the average doses of any antipsychotic medications, in terms of chlorpromazine equivalents, used by patients were similar (219 v. 206, respectively, t(137) = −0.49, P = 0.62). The difference remained non-significant when the analysis was limited to days on which antipsychotic medications were taken (291 v. 319, respectively; t(126) = 1.08, P = 0.28; n = 65 for clozapine and n = 63 for chlorpromazine). Additionally, there were no significant demographic or baseline clinical differences between the group of participants who remained on their originally assigned medication for the duration of the study (n = 29) and the group of participants who remained in the study for 9 years and switched medications (n = 95) (online Table DS2).

Efficacy

As previously reported,25 the clozapine group spent significantly more time in remission during the first year of the study and had a faster rate of remission in terms of psychopathological response during the first year of treatment. However, the average percentage of time that individuals spent in the three clinical states from years 2 through to 9 were essentially identical for the clozapine and chlorpromazine groups: 78% (remission), 8% (intermediate) and 14% (relapse) (Fig. 4). There were no statistically significant differences across groups in the average percentages of time spent in each clinical state or on any efficacy measure (i.e. BPRS, SANS, CGI-Ser dispose, GAF), either averaged over the entire study time period (i.e. years 2 through to 9) or at any individual follow-up time point (for example year 2, year 3) (Table 1). These results remained statistically non-significant after adjusting for baseline BPRS score, age at onset of psychotic symptoms, gender and DUP. In addition, there was no significant
effect of cumulative antipsychotic dose on improvement on the BPRS ($n = 139$, $t(1) = -0.07$, $P = 0.95$) nor was there an interaction effect between drug group (i.e. clozapine or chlorpromazine) and cumulative dosage ($t(1) = -0.02$, $P = 0.98$).

As a result of the similarities on outcome and efficacy measures between the clozapine and chlorpromazine groups, additional analyses were performed to determine the percentages of participants from the chlorpromazine group who took clozapine at some point during the 9-year study, and vice versa. Among individuals originally randomised to chlorpromazine, 30% (24/80) took clozapine at some point during the study; only 3.8% (3/80) of the clozapine group took chlorpromazine at some point during the study ($P < 0.01$). In addition, we determined the average percentages of time that participants in each group took other antipsychotic medications or resumed the original medication, and report them here descriptively: after discontinuing
Clozapine v. chlorpromazine in schizophrenia

After discontinuing clozapine ($n = 59$, median days 1895), chlorpromazine 51%, clozapine 7%, another first-generation antipsychotic 6%, another second-generation antipsychotic 13%, unspecified antipsychotic 51%, multiple antipsychotics 1%, no antipsychotic 73%.

Safety

Of 160 participants enrolled in the study, four (2.5%) developed agranulocytosis (two were randomised to clozapine and two were randomised to chlorpromazine). At the time that their agranulocytosis developed, one of these individuals was taking clozapine alone, one was taking chlorpromazine and trihexyphenidyl, and one was taking risperidone. The fourth person developed agranulocytosis while on aripiprazole.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Chlorpromazine</th>
<th>Clozapine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Psychiatric Rating Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>44.4 (11.7)</td>
<td>43.5 (10.9)</td>
<td>0.458</td>
</tr>
<tr>
<td>Year 1</td>
<td>21.6 (10.8)</td>
<td>21.2 (9.8)</td>
<td>0.276</td>
</tr>
<tr>
<td>Year 2</td>
<td>21.6 (9.8)</td>
<td>20.8 (9.3)</td>
<td>0.160</td>
</tr>
<tr>
<td>Year 3</td>
<td>21.7 (9.8)</td>
<td>20.7 (8.9)</td>
<td>0.164</td>
</tr>
<tr>
<td>Year 6</td>
<td>22.0 (10.3)</td>
<td>20.8 (9.3)</td>
<td>0.043</td>
</tr>
<tr>
<td>Year 7</td>
<td>22.0 (10.3)</td>
<td>20.8 (9.3)</td>
<td>0.041</td>
</tr>
<tr>
<td>Average (Y1–Y9)</td>
<td>22.0 (10.3)</td>
<td>20.8 (9.3)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

There were no statistically significant differences between the two groups on any efficacy measure for the follow-up time period.
clonazepam, and then while on clozapine along with aripiprazole and propranolol. The white blood cell counts of all of these people returned to normal with appropriate modification of their medications.

Of the 160 participants, a total of 26 (16%) developed tardive dyskinesia. Nine (11.3%) of these were randomised to clozapine and 17 (21.3%) were randomised to chlorpromazine (P = 0.02). Of the 21 individuals who remained on clozapine and the 8 who remained on chlorpromazine for the entire 9 years of this study, one person on clozapine (4.8%) developed tardive dyskinesia, as did two participants on chlorpromazine (25%) (P = 0.18). Each of these three participants was on antipsychotic monotherapy with either clozapine or chlorpromazine for the entire study period before development of their tardive dyskinesia, and one of the individuals in the chlorpromazine group had taken lorazepam, chlorpheniramine and benzhexol, each for 1–2 months, approximately 2 years before development of tardive dyskinesia.

Among the 29 participants who remained on either clozapine (n = 21) or chlorpromazine (n = 8) for the complete study, there were no significant differences in weight gain (clozapine 11.39 kg, chlorpromazine 12.74 kg, P = 0.79), white blood cell count (clozapine 5933, chlorpromazine 5225, P = 0.28), per cent of neutrophils (clozapine 64.3, chlorpromazine 62.4, P = 0.73), per cent of lymphocytes (clozapine 31.3, chlorpromazine 32.5, P = 0.82), ECG heart rate (clozapine 85, chlorpromazine 79, P = 0.49), ECG QT interval (clozapine 0.34, chlorpromazine 0.34, P = 0.98) or fasting glucose level (clozapine 6.8 mmol/l, chlorpromazine 5.8 mmol/l, P = 0.21) at the 9-year end-point.

Discussion

Main findings

This study extends the paper by Lieberman et al.40 on the first year of randomised treatment to either clozapine or chlorpromazine of 160 individuals with first-episode psychosis. In contrast to our hypothesis, we found that the initial exposure of individuals with first-episode psychosis to either chlorpromazine or clozapine did not alter the long-term outcome of their illness. Clozapine and chlorpromazine do not appear to have substantially differential effects on the long-term course of schizophrenia, and presumably therapeutic efficacy, when used as the initial treatment strategies in the first episode. Outcomes in individuals treated initially with clozapine and chlorpromazine were essentially identical on the primary outcome variable, remission status, and demonstrated minimal differences on all measures of psychopathology, including negative symptoms, at every follow-up time period (Table 1). The only differences in outcome were seen in treatment continuation and retention, and these are believed to reflect the relative tolerability of the medications. These results are consistent with the results reported for the first year of this study in that the advantages seen at 12 weeks for clozapine were not sustained at 52 weeks41 or thereafter. Finally, there was no effect of cumulative antipsychotic dosage on long-term outcome in this study.

The design of this study systematically addressed the question of whether clozapine has a putative disease-modifying effect (possibly neuroprotective) when administered in the first psychotic episode and confers a lasting value to individuals in (possibly neuroprotective) when administered in the first episode. Outcomes in individuals treated initially with clozapine and chlorpromazine for the entire 9 years of this study, one person on clozapine (4.8%) developed tardive dyskinesia, as did two participants on chlorpromazine (25%) (P = 0.18). Each of these three participants was on antipsychotic monotherapy with either clozapine or chlorpromazine for the entire study period before development of their tardive dyskinesia, and one of the individuals in the chlorpromazine group had taken lorazepam, chlorpheniramine and benzhexol, each for 1–2 months, approximately 2 years before development of tardive dyskinesia.

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Side-effects

Among the 29 individuals who remained on clozapine or chlorpromazine for the entire 9 years of the study, rates of tardive dyskinesia were greater in the chlorpromazine group, as expected,40 although it should be noted that this difference was not statistically significant, likely the result of the small sample size in this subsample. Second, agranulocytosis occurred only once among individuals treated with clozapine monotherapy, consistent with previous reports of the prevalence of agranulocytosis (approximately 1%).41 Finally, the degree of metabolic and other side-effects were similar between the two groups, which is consistent with the data on clozapine and chlorpromazine, both of which are known to induce metabolic effects.42,43

Limitations

There are several limitations to this study. Participants were in open, naturalistic treatment for the majority of the follow-up period after initially receiving randomised, double-blind treatment, and there was notable crossover between the two groups. This naturalistic treatment may also have confounded the effect of dosing on long-term outcome.
Implications

In terms of the question, does the type of antipsychotic medication to which a patient is first exposed influence their long-term outcome, regardless of the type of treatment to which they are later exposed, the answer from this study appears to be no. To the extent that there are any differences, these appear to be related to side-effects and tolerability and not therapeutic efficacy. The findings from this 9-year investigation of treatment-naïve, first-episode participants originally randomised to clozapine or chlorpromazine suggest that the long-term outcomes of individuals with first-episode psychosis are no different whether their initial exposure is to clozapine or chlorpromazine. Further, these findings support the growing body of literature that shows few differences in effectiveness between antipsychotic medications in non-treatment refractory schizophrenia.

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References


### Data supplement

#### Table DS1  Baseline demographic data for the two groups

<table>
<thead>
<tr>
<th></th>
<th>Clozapine group (n = 80)</th>
<th>Chlorpromazine group (n = 80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: male/female</td>
<td>43/37</td>
<td>41/39</td>
<td>0.87</td>
</tr>
<tr>
<td>Age at onset of psychosis, years: mean (s.d.)</td>
<td>27.1 (6.1)</td>
<td>27.2 (6.8)</td>
<td>0.86</td>
</tr>
<tr>
<td>Duration of untreated psychosis, months: mean (s.d.)</td>
<td>17.7 (16.7)</td>
<td>19.7 (19.0)</td>
<td>0.49</td>
</tr>
<tr>
<td>Age at admission, years: mean (s.d.)</td>
<td>28.5 (6.5)</td>
<td>28.7 (7.2)</td>
<td>0.85</td>
</tr>
<tr>
<td>Baseline Brief Psychiatric Rating Scale score, mean (s.d.)</td>
<td>43.3 (5.1)</td>
<td>44.4 (5.1)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

* a. n = 79 for the chlorpromazine group.

#### Table DS2  Baseline demographic data for the 29 participants who remained on the medication to which they were originally assigned for the entire 9-year study period and the 95 participants who remained in the study but switched medications

<table>
<thead>
<tr>
<th></th>
<th>Remained on original medication (n = 29)</th>
<th>Switched medication during study (n = 95)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: male/female</td>
<td>19/10</td>
<td>46/49</td>
<td>0.14</td>
</tr>
<tr>
<td>Age at onset of psychosis, years: mean (s.d.)</td>
<td>26.9 (6.6)</td>
<td>26.8 (6.6)</td>
<td>0.97</td>
</tr>
<tr>
<td>Duration of untreated psychosis, months: mean (s.d.)</td>
<td>16.8 (19.2)</td>
<td>19.7 (17.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Age at admission, years: mean (s.d.)</td>
<td>28.2 (7.2)</td>
<td>28.4 (7.0)</td>
<td>0.90</td>
</tr>
<tr>
<td>Baseline Brief Psychiatric Rating Scale score, mean (s.d.)</td>
<td>43.4 (4.2)</td>
<td>44.0 (5.3)</td>
<td>0.51</td>
</tr>
</tbody>
</table>
Clozapine v. chlorpromazine in treatment-naive, first-episode schizophrenia: 9-year outcomes of a randomised clinical trial
Ragy R. Girgis, Michael R. Phillips, Xiaodong Li, Kejing Li, Huiping Jiang, Chengjing Wu, Naihua Duan, Yajuan Niu and Jeffrey A. Lieberman

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